American Journal of Public Health
and THE NATION'S HEALTH

Volume 31 June, 1941 Number 6

Rapid Treatment of Early Syphilis With Multiple Injections of Mapharsen

Preliminary Report of 275 Cases Treated with Mapharsen Alone and 141 Cases Treated with Mapharsen and Fever *

EVAN W. THOMAS, M.D., AND GERTRUDE WEXLER, M.D.

Department of Dermatology and Syphilology, New York University College of Medicine, and the Department of Dermatology and Syphilology, Third Medical Division (New York University), Bellevue Hospital, New York, N. Y.

MANY attempts have been made to use massive arsenotherapy for the rapid cure of syphilis. Until recently these were all abortive because of the toxic effects of the drugs. Even with the aid of the continuous intravenous drip, devised by Hyman, Chargin, and Leifer [1] in 1933, neoarsphenamine was toxic, peripheral neuritis being one of the most frequent complications. Recently, however, these same investigators in association with a committee, appointed by Commissioner John L. Rice of the New York City Department of Health, found that arsenoxide or mapharsen given in massive dosage by the drip method caused appreciably fewer toxic effects than neoarsphenamine.[2]

The use of mapharsen has theoretical advantages for massive dosage which are not shared by other trivalent arsenical drugs: (1) As arsenoxide is the effective spirochetocidal derivative of all the arsphenamines, its direct use requires smaller amounts of arsenic for effective dosage. (2) A higher percentage of the arsenic can be recovered in the excreta after mapharsen is used than after neoarsphenamine.[3] (3) The elimination of arsenic is more rapid with mapharsen than with either arsphenamine or neoarsphenamine.[3] (4) As mapharsen is less sensitizing than other arsphenamines, exfoliative dermatitis is almost never encountered with its use.[4]

In 1937, in the wards of Bellevue Hospital we began to increase the number of mapharsen injections in patients with early syphilis from 1 a week to 2. By 1938 we were giving 3 injections a week of 0.06 gm. mapharsen for 4 weeks to all patients with early infectious syphilis. This was followed by the usual routine treatment with courses of weekly injections of bismuth alternating with courses of arsenical drugs. In the light of this experience and after observing the use of mapharsen by the

* Aided in part by a grant from the American Committee on Research in Syphilis.

intravenous drip method at Mt. Sinai Hospital, we determined in December, 1939, to attempt rapid massive treatment without using the continuous drip, for which we had no facilities at Bellevue Hospital. With few exceptions, only patients with early infectious syphilis were chosen for this experimental treatment and all were hospitalized.

SURVEY OF METHODS OF TREATMENT

We started our intensive treatment by giving 2 injections of 0.06 gm. mapharsen daily for 10 days. Every dose was dissolved in 10 cc. of sterile distilled water and given intravenously by the usual syringe technic. From 6 to 8 hours intervened between the morning and evening doses. After treating 38 patients in this manner the period of treatment was shortened from 10 to 6 days because of the occurrence of a number of early acute arsenical erythemas which forced us to interrupt treatment on the 7th or 8th day. Apart from this reaction all patients had tolerated the treatment so well that we decided not to lower the total amount of drug but to increase every dose from 0.06 gm. to 0.1 gm. and to give the drug twice a day for 6 days. As women had tolerated the 10 day treatment with a total dosage of 1.2 gm. as well as men, we made no distinction in dosage between the sexes in the 6 day treatment.

Except for some nausea and vomiting this treatment was tolerated remarkably well until the 111th case, a 23 year old Italian woman, died from hemorrhagic encephalitis. After long and anxious consultation we decided to continue the 6 day treatment but to reduce the dosage of mapharsen and to increase our efforts to observe the progress of each patient by more thorough laboratory study. Thus in males each individual dose of mapharsen was reduced to 0.08 gm. or 0.09 gm. instead of 0.1 gm.; and in females to 0.06 gm. or 0.07 gm. The total dosage, therefore, varied from 0.72 gm. to 1.08 gm. in 6 days. In addition to the usual blood counts, blood chemistry and liver function tests, careful spinal fluid examinations were made on each patient before and immediately after treatment.

In spite of increased watchfulness and care, in September, 1940, we had another case of hemorrhagic encephalitis following the 11th injection of 0.09 gm. mapharsen in 5½ days. This patient was a 26 year old Italian male who had tolerated his treatment fairly well except for marked apprehensiveness and worry over the nature of his disease. His temperature rose on the morning of the 5th day of treatment and a spinal tap was done. This showed xanthrochromic fluid and a total protein of 100 mg. per cent, the upper limit of normal by our method being 20 mg. per cent. Apart from the temperature he had no symptoms at that time but the spinal fluid findings made us very uneasy. Our ignorance of the pathogenesis and treatment of hemorrhagic encephalitis, however, is so great that we failed to prevent the onset of symptoms which started about 4.30 on the afternoon of the same day. Spinal drainage had been a complete failure in our first case of hemorrhagic encephalitis and no attempt was made to repeat it. This patient was desperately ill for about 48 hours. At the end of this time he was obviously out of danger except for an aspiration pneumonia which was controlled by sulfapyridine. He is now well and has a negative serology as well as normal spinal fluid.

About the same time a possible third case of hemorrhagic encephalitis developed in a Polish boy, 21 years of age. After the 11th injection of 0.07 gm. mapharsen in 5½ days he had 3 brief convulsive seizures, each lasting about 30 seconds. His spinal fluid findings were normal on that day and he

had no symptoms or complaints apart from his brief seizures. Five days later he had 2 more similar seizures. On this day his spinal fluid showed a total protein of 40 mg. per cent. He gave no history of epilepsy and he has had no further seizures.

COMBINED FEVER AND CHEMOTHERAPY

By this time we had treated 226 patients with mapharsen alone. Apart from the cases of hemorrhagic encephalitis the treatment had proved satisfactory from the point of view of the patient's tolerance and the ease with which it was given. We had learned, however, that no laboratory tests or clinical observations within our scope gave us any aid in anticipating hemorrhagic encephalitis, and we concluded that the incidence of this complication was too high for further experimentation with intensive mapharsen alone. Therefore, we turned to a combination of fever and mapharsen as a possible means of avoiding hemorrhagic encephalitis.

As long ago as 1923, Kyrle, Dattner,[5] and others noted that fever seemed to prevent toxic reactions to arsenical drugs in the treatment of syphilis. More recently de Kruif and Simpson[6] have made similar observations. At Bellevue Hospital we had noted that elderly patients treated with malaria for neurosyphilis tolerated daily injections of marpharsen following their course of fever amazingly well. In addition to these observations it is known that fever seems to aid the effectiveness of arsenical drugs in the treatment of syphilis. Consequently, besides hoping to avoid the occurrence of hemorrhagic encephalitis by the use of fever, it seemed justifiable to attempt the cure of early syphilis with a smaller total dosage of mapharsen, if this was used in association with fever. The plan of treatment adopted was as follows:

2 injections of 0.06 gm. mapharsen on the first day.
1 injection 0.06 gm. mapharsen on each day thereafter for 7 days.
On the 2nd, 4th, 6th, and 8th days fever was induced by typhoid vaccines intravenously. In order to prolong the fevers at a level of 104° F. or over for at least 4 hours 2 injections of typhoid vaccines were usually required. This made a total dosage of 0.54 gm. mapharsen and 4 fevers in 8 days.

No serious complications were encountered with this method of treatment in a series of 125 patients. We cannot tell as yet, however, whether the therapeutic results with only 0.54 gm. mapharsen will prove as satisfactory as with larger doses. So far Wassermann titers seem to have responded well, but the association of typhoid vaccines intravenously and mapharsen on the same day causes much distress to many patients, headaches, nausea and vomiting forming the chief complaints.

In the hope of decreasing the discomfort of treatment we recently altered our program. The number of fevers was reduced from 4 to 2 and they are

TABLE 1

Distribution of Patients by Age, Sex, Race

	All Patients			*White*			*Negro*			*Others*		
Age in Years	*Total*	*M.*	*F.*	*Total*	*M.*	*F.*	*Total*	*M.*	*F.*	*Total*	*M.*	*F.*
10–19	55	19	36	10	6	4	44	12	32	1	1	0
20–29	215	126	89	79	50	29	126	70	56	10	6	4
30–39	89	66	23	48	35	13	36	28	8	5	3	2
40–49	30	24	6	20	15	5	8	8	0	2	1	1
50+	8	8	0	8	8	0	0	0	0	0	0	0
Total	397	243	154	165	114	51	214	118	96	18	11	7

not given on the same days with mapharsen. In addition, the total dosage of mapharsen has been increased from 0.54 gm. to 0.84 gm. or more in selected cases. The program calls for 8 days of treatment which is given as follows:

2 injections of 0.07 gm. mapharsen on the 1st day.
Fever induced by typhoid vaccines on the 2nd day.
2 injections of 0.07 gm. on the 3rd day
Fever induced by typhoid vaccine on the 4th day.
4 days of 0.07 gm. mapharsen twice daily.

Although only a few cases have been treated in this way to date, there seems to be less discomfort than with the previous method. Obviously there are many possible combinations of fever and arsenotherapy. Our aim is to find the one which gives a minimum of discomfort and a maximum of safety with, of course, satisfactory therapeutic results.

Because we occasionally encounter patients in whom fever seems to be contraindicated, as in pregnant women or active pulmonary tuberculosis, we have not entirely abandoned intensive treatment with mapharsen alone.

ANALYSIS OF CASES TREATED

Reference to Tables 1 and 2 will show that the series of cases treated in no sense represents a selected group. At times we feared that we were using too little caution in this respect, but no patient was treated against his or her wishes and every precaution was taken to interrupt or stop therapy when this seemed indicated. The majority came from the poorest groups in New York City; many had varying degrees of malnutrition and mild anemias; associated diseases of an acute or chronic nature were not uncommon as is shown in Table 2. We experienced surprisingly little difficulty, however, in treating these patients. Very few of those who might have been considered poor risks when admitted to the wards had unfavorable reactions, and many of them stated that they felt better after treatment than for a long time before treatment. Six pregnant women who presented themselves with early infectious syphilis were included in our series. In no case was fever attempted in these patients. Three have been delivered since their treatment was completed. Detailed reports of results will be made later.

TABLE 2

Diseases Associated with Syphilis in the Cases Treated

	No. of Cases
Gonorrhea	44
Chancroid	17
Lymphogranuloma inguinale	6
Granuloma inguinale	4
Balanitis	2
Condyloma acuminatum	5
Pulmonary tuberculosis	5
Essential hypertension	1
Rheumatic heart disease (inactive)	2
Chronic bronchitis & emphysema	1
Appendicitis	2
Appendectomy before treatment	1
Appendectomy interrupting treatment	1
Chronic alcoholism (severe)	8
Epilepsy	1
Anal fistula	3
Alveolar abscess (severe)	1
Acute sinusitis (severe)	1
Infected pilonidal cyst	1
Adenoma of thyroid	1
Previous thyroidectomy	1
Schizophrenia	1
Pregnancy	6

TABLE 3

Distribution of Treatment Courses by Stage of Disease

Total No. of treatment courses	416
Primary and secondary syphilis	380
Early latent syphilis	17
Retreatments *	19

* These consist of cases originally treated by the rapid syringe method for early infectious syphilis. Eighteen were retreated because of relapses or reinfections and 1 because of a persistently positive Wassermann test over a period of 9 months.

TABLE 4

Distribution of Cases by Type of Treatment

Total No. of Treatment Courses from Dec. 1939 to Mar. 15, 1941	416
Treated with mapharsen only	275
Treated with mapharsen and typhoid vaccine	140
Treated with mapharsen and artificial fever	1

TABLE 5

Comparison of Toxic Effects in Cases Treated with Mapharsen Only—Syringe Method (Bellevue Hospital) and Intravenous Drip Method (Mt. Sinai Hospital) [2]

	Syringe Method (Bellevue)		*Intravenous Drip Method (Mt. Sinai)*	
	No.	*Per cent*	*No.*	*Per cent*
Total treatment courses	275	100.0	288	100.0
Herxheimer or primary fevers	88	32.0	116	40.0
Secondary rises in temperatures	27	9.8	36	12.0
Slight temperature elevation throughout treatment	5	1.8	*	*
Exfoliative dermatitis	0	0.0	0	0.0
Early acute arsenical erythemas and urticarias	19	6.9	33	11.0
Pruritis (few hours duration)	15	5.5	*	*
Nitritoid (after 10th mapharsen in one patient)	1	0.36	0	0.0
Marked vomiting	18	6.5	*	*
Diarrhea (mild)	7	2.5	*	*
Headaches (mild)	56	20.4	*	*
Icteric index elevation during treatment (transient)	3	1.08	*	*
Jaundice during hospitalization	0	0.0	2	0.7
Toxic hepatitis (etiology uncertain), 6 months after treatment	1	0.36	1	0.34
Blood N.P.N. elevation during treatment	0	0.0	*	*
Blood dyscrasias	0	0.0	0	0.0
Peripheral neuritis within few weeks after treatment (no objective signs)	2	0.72	5	1.6
Cerebral symptoms (total)	3	1.08	3	1.04
Hemorrhagic encephalitis	2	0.72	1	0.34
Single convulsion	0	0.0	1	0.34
Disorientation	0	0.0	1	0.34
Epileptiform convulsive seizures	1	0.36	*	*
Treatment interrupted due to secondary rise in temperature or marked vomiting	20	7.3	*	*
Treatment stopped between 0.6 and 1.0 gms. mapharsen	8	2.9	*	*
Due to secondary rise in fever	3	1.08	*	*
Due to secondary rise in fever associated with marked vomiting	4	1.5	*	*
Due to tachycardia in a patient with suspected hyperthyroid disease	1	0.36	*	*
Fatality (due to hemorrhagic encephalitis)	1	0.36	0	0.0

* No information given.[2]

TOXIC MANIFESTATIONS

From Table 5 it will be seen that the toxic effects in the patients receiving only mapharsen roughly parallel those in the series treated by the intravenous drip method at Mt. Sinai Hospital. Apart from hemorrhagic encephalitis none of these manifestations warrants abandoning further experimentation with this type of treatment. After the first 2 days of injections patients were allowed out of bed and no attempt was made to alter the regular ward diet.

Table 6 gives the toxic effects noted in the series receiving combined mapharsen and fever treatment. Among this group are found the only patients who showed transitory evidence of possible renal damage. Three had elevated non-protein nitrogen associated with marked albuminuria and cylindruria. In every case these abnormal findings disappeared entirely within a few days after treatment was finished. Four patients became mildly delirious at the height of their fevers but they had temperatures of over 106° F. at the time. Electrocardiographic tracings were made in a number of patients at various intervals during treatment. Those patients receiving only mapharsen showed no changes in their electrocardiograms. In the series where mapharsen was combined with fever transitory electrocardiographic changes were not infrequent. Four patients in the typhoid vaccine series had daily electrocardiograms before, during, and after treatment. Two showed T wave changes in leads I and II on the days when they had fever. This was to be expected as it is well known that fever treatments may cause transient electrocardiographic changes.

Mention must also be made of the

TABLE 6

Toxic Effects in Series Treated with Mapharsen and Typhoid Vaccines

	Number	*Per cent*
Total treatment courses	140	100.0
Herxheimer or primary fevers	53	37.8
Secondary rises in temperature	6	4.3
Exfoliative dermatitis	0	0.0
Early acute arsenical erythemas & urticarias	11	7.8
Severe headaches	123	88.0
Delirium or confusion (temperature over 106° F.)	4	2.9
Marked vomiting	97	69.0
Diarrhea	6	4.3
Icteric index elevation during treatment (transient)	7	5.0
Jaundice (total no.)	2	1.4
during hospitalization	1	0.71
3 weeks after treatment	1	0.71
Blood NPN elevation during hospitalization (transient)	3	2.14
Blood dyscrasias	0	0
Peripheral neuritis	0	0
Generalized aches and pains	49	35.0
Palpitation or precordial distress	6	4.3
Persistence of temperature over 12 hours	7	5.0
Treatment interrupted (total no.)	7	5.0
due to secondary rise in temperature	2	1.4
due to persistent fever after typhoid vaccine	3	2.14
due to acute appendicitis	1	0.71
due to infected pilonidal cyst	1	0.71
Less than 4 fevers given (total no.)	19	13.6
due to reactions—mainly vomiting and headaches	18	12.9
due to pulmonary tuberculosis	1	0.71
Hemorrhagic encephalitis	0	0.0
Fatalities	0	0.0

incidence of mild transitory liver damage in the series receiving typhoid vaccines intravenously. Seven had increased icteric indices and 22 per cent showed an increase of urobilinogen at some time during treatment. None of the abnormalities noted, however, remained more than a few days after treatment ended. Clinical jaundice of a few days' duration occurred in 2 patients but enlargement of the liver was not found during or after treatment in any case.

In summary, it is evident that the combination of intravenous typhoid vaccine and mapharsen, especially when both are administered the same day, gives more frequent transitory toxic effects than mapharsen alone, but no clinical evidences of hemorrhagic encephalitis were noted in 141 cases. By reducing the number of fevers and omitting mapharsen on the days when fever is given, we believe that the incidence of minor toxic effects can be materially reduced.

LABORATORY STUDIES

Space prevents a detailed discussion of the laboratory findings in this large series. Over 100 cases had complete hematological studies immediately before and during, or right after treatment. These included cell volume and hemoglobin determinations, red and white cell counts with careful differential, platelet and reticulocyte counts, cell fragility tests, bleeding and coagulation time, quantitative bilirubin determinations and erythrocyte sedimentation rates. The studies were made by Drs. Leonard Goldwater and David H. Goldstein, New York University College of Medicine, with the aid of a trained technician, and will be reported by them in a later paper. It is of special interest that in the hemorrhagic encephalitis cases, apart from spinal fluid findings, all laboratory tests, including blood vitamin C determinations, were negative.

Arsenic Content in the Blood: Blood arsenic determinations were made twice a day on over 30 patients. In a few

instances these were checked in two different laboratories by two different technicians. In general, the arsenic levels in the blood gradually rose during treatment, and the curves are similar to those obtained at Mt. Sinai Hospital, where the intravenous drip was used. Complete reports of these studies will be made later by Drs. Goldwater and Goldstein.

Spinal Fluid Findings: The results of spinal fluid tests done immediately before and after treatment are given in Tables 7 and 8. They merit study and discussion but space permits only a few comments. It will be noted (Table 8) that, in addition to the hemorrhagic encephalitis cases, 4 patients had marked abnormalities in their spinal fluids following treatment, although 3 of them had normal findings prior to treatment. One patient had a positive Wassermann test in the higher amounts of spinal fluid before therapy but the Wassermann reaction became negative following treatment. The cells and protein, however, increased. It is difficult to explain the pleocytosis and increased protein in these 4 cases for a number of reasons: (1) They were associated with no clinical signs or symptoms. (2) The fluids continued to be abnormal for considerable lengths of time following treatment, which is contrary to the findings in hemorrhagic encephalitis. (3) In no case was the Wassermann reaction positive after treatment. Presumably we are, therefore, dealing with treatment reactions rather than syphilis. Three of these cases received typhoid vaccines and mapharsen. One woman who received 0.66 gm. mapharsen without fever was kept in the hospital for 9 weeks following treatment in order to check her spinal fluid at intervals, but she still had increased cells and protein on discharge. Her blood serology is now negative but she stubbornly refuses further spinal taps because she feels well.

TABLE 7

Positive Spinal Fluids before Treatment *

	No. of Fluids Examined		*Positive ** and Doubtful ****: *Total*		*Positive*		*Doubtful*		*Negative*	
Stage of Disease	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Seronegative Primary Syphilis	12	100	0	0.0	0	0.0	0	0.0	12	100.0
Seropositive Primary Syphilis	42	100	5	11.9	3	7.1	2	4.8	37	88.1
Secondary Syphilis	213	100	48	22.5	36	16.9	12	5.6	165	77.5
Total	267	100	53	19.8	39	14.6	14	5.2	214	80.2

* Of the 53 positive and doubtfully positive spinal fluids, 50 were examined immediately after treatment. The changes after treatment were not significant except for the one case shown in Table 8.

** Positive spinal fluids include those with more than 15/3 cells, usually accompanied by elevations of total protein and colloidal gold changes. Of the 39 positive spinal fluids, 16 or 41 per cent had positive spinal fluid Wassermann reactions.

*** Doubtful spinal fluids include those with 12/3 to 15/3 cells accompanied by slight elevations of total protein and slight colloidal gold changes.

FOLLOW-UP OF PATIENTS

From the beginning of this experiment it was clear that we would be unable to follow a number of our patients for any length of time after treatment was completed. Our records show that 33 per cent are lost at present. Some of them had negative serological findings when last seen; 6 reported to out-of-town clinics or institutions where routine therapy was given because the blood Wassermann test was found to be positive. Patients are given letters to show physicians in charge of other clinics but they either lose the letters or the information is disregarded.

TABLE 8

Changes after Treatment in Initially Negative Spinal Fluids

	No.	*Per cent*
Total number examined before and after treatment *	183	100.0
Definite but slight changes after treatment	37	20.2
Marked changes after treatment	6	3.3
No change after treatment	140	76.5

Details of Findings in Seven ** Cases showing marked changes:

Case	*Time of Examination*	*Wass.*	*Cells****	*Pandy*	*Total Protein*****	*Colloidal Gold*
Hemorrhagic enceph.—0.9 gm. maph.	Onset of hemorrhagic encephalitis	4+4+4+	6/3	4+	over 200	1233454321
Hemorrhagic enceph.—0.99 gm. maph.	Before treatment	neg.	0	neg.	14	0000000000
	5 hrs. before onset of hemorrhagic enceph.	neg.	168/3	4+	100	0123211000
	2 days later	QNS	many RBC******	4+	55	QNS
	17 days later	neg.	30/3	1+	26	QNS
	5 months later	neg.	0	neg.	5	0000000000
Epileptiform seizures—0.77 gm. maph.	Before treatment	neg.	6/3	neg.	10	0000000000
	Onset of seizures	neg.	8/3	trace	22	0000000000
	5 days later	4+neg. neg.	60/3	2+	43	0011221000
	9 days later	neg.	64/3	trace	27	0000000000
	2½ months later	neg.	1/3	neg.	5	0000000000
No cerebral manifestations 0.66 gm. maph.	Before treatment	neg.	6/3	neg.	11	0001112100
	16 days after treatment	neg.	390/3	4+	80	1123432100
	23 days after treatment	neg.	180/3	4+	45	1233221000
	7 weeks after treatment	neg.	90/3	4+	45	1221000000
	9 weeks after treatment	neg.	75/3	4+	QNS	1221000000
No cerebral manifestations 0.54 gm. maph. & 4 typhoid vacc.	Before treatment	neg.	1/3	neg.	16	0000000000
	2 days after treatment	neg.	450/3	2+	38	0012110000
	18 days after treatment	neg.	120/3	1+	40	0000000000
No cerebral manifestations 0.48 gm. maph. & 2 typhoid vacc.	Before treatment	neg.	2/3	neg.	8	0000000000
	8 days after treatment	neg.	41/3	4+	60	1233321100
	17 days after treatment	neg.	53/3	2+	33	0011100000
	24 days after treatment	neg.	25/3	neg.	24	0011000000
No cerebral manifestations 0.54 gm. maph. & 4 typhoid vacc.	Before treatment	4+ + neg.	many RBC******	neg.	18	0000000000
	1 day after treatment	4+ ± neg.	many RBC****** and WBC	±	21	0112210000
	4 days after treatment	+ ± neg.	150/3	2+	75	0112210000
	11 days after treatment	neg.	62/3	±	22	0111100000

* Of the 267 cases shown in Table 7, 233 had spinal fluid examinations before and after treatment. Of these 233 cases, 183 had initially negative spinal fluids.

** Because of similar findings to the other 6 cases, an initially positive spinal fluid is included in this table.

*** With the Fuchs-Rosenthal chamber, the total number of cells in 3 cu. mm. are counted; consequently, to express this result in the conventional fashion of cells per cu. mm., it is necessary to divide the result by 3. For example, if the chamber count were 6 cells, this would be equivalent to 6/3 or 2 cells per cu. mm.

**** Total proteins are determined by the method of Exton and Rose using the "junior scopometer." The normal limit of total proteins by this method is approximately 20 mg. per 100 cc.

***** Spinal fluids were clear, but microscopic examination showed many R.B.C.

Some of the missing patients may still be found as we have assurance of more help to trace them in the future.

The question naturally arose whether patients should receive the rapid treatment when it was obvious that they would not report for follow-up observation. We decided that from a public health standpoint it was better to treat them intensively than to turn them loose after a few injections of arsenical drugs. Past experience indicated that, if we could not follow them after discharge, most of them would not continue routine therapy.

RESULTS OF TREATMENT

Because the combined treatment with

TABLE 9

Status of 142 Cases, 6 to 15 Months after Treatment with 1.08 gm. to 1.2 gm. Mapharsen

Status before Treatment	No. Treated	Status 6 to 15 Months after Treatment: Now Seronegative	Almost Seronegative *	Still Seropositive	Relapse or Reinfection	Lost
Seronegative primary syphilis	6	1	0	0	1	4
Seropositive primary syphilis	28	17	2	0	2	7
Secondary syphilis	108	55	7	3	7	36
Total	142	73	9	3	10	47

Summary

	Number	Per cent
Cases treated	142	100.0
Lost	47	33.1
Followed	95	66.9
Status of 95 cases followed		
Probable favorable results	82	86.3
Now seronegative (73 cases or 76.8%)		
Almost seronegative (9 cases or 9.5%)		
Still seropositive	3	3.2
Relapse or reinfection	10	10.5
Total	95	100.0

* Cases listed as almost seronegative have Wassermann titers of less than 10 and the Bellevue Hospital Wassermann test is entirely negative in all but 2 cases.

fever and mapharsen was started less than 6 months ago, the results of treatment are reported only on those patients who received massive dosage with mapharsen alone. They are reported in Tables 9, 10, and 11. Early latent cases are omitted.

Favorable Results: Of the patients followed for 6 months or more 86.5 per cent now have a negative or almost negative serology. This percentage includes 4 cases successfully re-treated because of relapses or reinfections after their original intensive treatment. Through the courtesy of Dr. Wadsworth of the New York State Health Department, Wassermann tests are titered in the State Laboratory to the end point in the patients of this series. Some titers of over 600 have been reported. The

TABLE 10

Status of 59 Cases, 6 to 15 Months after Treatment with 0.66 gm. to 0.84 gm. Mapharsen

Status before Treatment	No. Treated	Status 6 to 15 Months after Treatment: Now Seronegative	Almost Seronegative *	Still Seropositive	Relapse or Reinfection	Lost
Seronegative primary syphilis	4	2	0	0	1	1
Seropositive primary syphilis	4	3	0	1	0	0
Secondary syphilis	51	18	7	2	5	19
Total	59	23	7	3	6	20

Summary

	Number	Per cent
Cases treated	59	100.0
Lost	20	33.9
Followed	39	66.1
Status of 39 cases followed		
Probable favorable results	30	76.9
Now seronegative (23 cases or 59%)		
Almost seronegative (7 cases or 11.9%)		
Still seropositive	3	7.7
Relapse or reinfection	6	15.4
Total	39	100.0

TABLE 11

Summary of Cases in Tables 9 and 10 Status of the 134 Cases Treated with 0.66 gm. to 1.2 gm. Mapharsen and Kept under Observation 6 to 15 Months

	No.	Per cent
Probable favorable results *	112	83.6
Still seropositive	6	4.5
Relapse or reinfection	16	11.9
Total	134	100.0

* One of the seropositive cases and 14 of the relapses or reinfections have been re-treated by the rapid syringe method. Four of them are already seronegative. Including these 4, we have a total of 116 cases. or 86.5 per cent, with probable favorable results.

cases listed as almost negative have titers of less than 10 and the Bellevue Hospital Wassermann test is entirely negative in all but 2.

It will be noted that the percentage of favorable results is higher in the series treated with over 1 gm. mapharsen. With this dosage 86.3 per cent of those originally treated have favorable results. Only 76.9 per cent of those treated with a total dosage of 0.6 gm. to 0.84 gm. have similar results. The difference in percentages is possibly more apparent than real but, in view of a somewhat similar finding in the Mt. Sinai Hospital series, it may be significant.

Spinal fluids examined from 6 to 12 months after treatment in 98 patients were completely negative. Nine of them had positive spinal fluids prior to treatment.

Persistently Positive Serology: Six patients are listed as having strongly positive Wassermann tests over 6 months after treatment. One has already been re-treated with fever and mapharsen. The other 5 are still pending. Four may yet become negative because their titers continue to fall. The other case is now considered a treatment failure and is being admitted to the wards for re-treatment.

Relapses or Reinfections: An analysis of these cases would require a paper in itself. If we were to hazard a guess, we would list 8 and possibly 10 of the 16 as possible reinfections. Two were seronegative at the time of their original treatment. One remained negative for 6 months before returning with a penile lesion of 2 weeks' duration, a maculopapular rash of 2 days' duration, and a strongly positive blood Wassermann test. The other patient remained seronegative for 3 months and then returned with a dark-field positive penile chancre. His Wassermann titer at that time was 6. It increased to 33 during his retreatment but has since become negative. In addition to these originally seronegative cases, 4 other patients had become seronegative before new infectious lesions appeared. They all admitted frequent sexual exposures after their original treatment. As a matter of fact, 14 of the 16 patients gave histories of exposures prior to the reappearance of new lesions. In 4 instances we were able to find and examine the probable sources of reinfection. All 4 had active infectious lesions. Two patients admitted returning to the same person to whom they had been exposed before their first infection. Their serology remained positive up to the time of the appearance of new lesions. Both of their possible sources of reinfection were found by us to have secondary syphilis of long standing. From our present knowledge it is impossible to determine whether these cases represent reinfections or relapses.

Among the patients whom we regard as relapses was one who had originally

TABLE 12

Spinal Fluid Examinations 6 to 12 Months after Treatment *

	No.	Per cent
Total number examined	98	100
Positive Spinal fluids	0	0
Negative Spinal fluids	98	100

* 9 cases in this group had positive spinal fluids before treatment.

been treated by the drip method at Mt. Sinai Hospital and returned to us in May, 1940, with primary and secondary lesions. He was re-treated by our method only to return in October with dark-field positive lesions on his penis. He was re-treated once again but is now lost. Two patients admitted no sexual exposure prior to the appearance of relapsing lesions. Another patient was reported to have relapsed in prison but he admitted exposure prior to his imprisonment. Fourteen of the 16 cases who relapsed or were reinfected have been re-treated. Four are now completely negative and the Wassermann titers of the other cases followed seem to be responding satisfactorily.

The problem of relapse and reinfection cannot be dismissed without noting that of the 380 infectious cases treated by our rapid methods to date, 23 gave a history of previous early syphilitic lesions and treatment. Three had been treated adequately in our own clinic by routine therapy and their serological findings had been negative for well over 1 year. The others were chiefly instances of inadequate therapy.

DISCUSSION

From our series of 275 patients treated intensively with mapharsen, it appears that this drug can be given in massive dosage with a minimum of toxic effects. Clearly the incidence of hemorrhagic encephalitis is too great for further experimentation at present with the higher dosages of mapharsen we at first used. Both at Mt. Sinai Hospital and at Bellevue Hospital the severe cases of hemorrhagic encephalitis occurred in patients who received a total of at least 0.9 gm. mapharsen, or 4.0 gm. neoarsphenamine. This suggests but does not prove that the dosage is the chief factor involved. Combined with fever, a total dosage of 0.54 gm. to 0.6 gm. mapharsen was given to 141 cases without causing any signs of hemorrhagic encephalitis. We are unable to determine at present whether the results of the combined therapy will be as satisfactory as those of the larger doses of mapharsen alone, but so far our experience with combined treatment is encouraging.

We have found that it requires, on an average, 4 to 6 months following treatment for the blood Wassermann test to become negative. In some instances it may require a year or more before complete serological reversal is achieved. In general the longer a patient has had syphilis, the longer it takes for the blood Wassermann test to become negative, although there are exceptions to this rule.

The incidence of positive spinal fluids in our patients, prior to treatment, is lower than that usually recorded. We found, however, that immediately following treatment, 20 per cent of the previously negative spinal fluids showed some increase in cells or protein, and in some instances the Wassermann reaction became positive in the larger amounts of fluid. We believe that this can be explained by the actual presence within the central nervous system of a syphilitic inflammatory process which is temporarily activated by treatment. Complete healing occurs, because spinal fluids examined 6 to 12 months later were negative in every case. The possibility that the spinal fluid abnormalities, noted immediately after therapy, represent toxic reactions to arsenic must be considered in view of the 4 unusual cases previously cited. In our opinion, however, these 4 belong to a separate group.

Analysis of our results proves once more that there is no panacea for early syphilis. The intensive method of treatment may not be to blame for some of the cases we listed as "treatment failures." Before our results can be compared adequately with routine therapy more time must elapse and many fac-

tors must be considered, including the failure of patients to persist with routine treatment. It is also too soon for a scientific comparison between the therapeutic results of the intravenous drip method and the methods used by us. It seems, however, that the continuous drip has no special therapeutic advantages over intensive treatment by multiple injections. Obviously, rapid methods of treatment are still in the experimental stage and much remains to be done before any of them can be accepted as reliable and safe, but our experience should encourage their further study.

REFERENCES

1. Chargin, L., Leifer, W., and Hyman, H. T. The Application of the Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in the Treatment of Early Syphilis. *J.A.M.A.*, 104:878 (Mar. 16), 1935.

2. Chargin, L. Toxicological Manifestations of Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method. *Arch. Dermat. & Syph.*, 42:247 (Aug.), 1940.

3. Sobotka, H., Mann, W., and Feldbau, E. Arsenic Excretion in the Urine and Concentration in the Blood. *Arch. Dermat. & Syph.*, 42:270 (Aug.), 1940.

4. Epstein, E. Cutaneous Toxicity of Mapharsen. *Am. J. Syph., Gonor. & Ven. Dis.*, 25:225 (Mar.), 1941.

5. Dattner, Bernhard. Probleme und Ergebnisse der Paralysebehandlung. *Klin. Wchnschr.*, III, 5:177, 1923.

6. de Kruif, P., and Simpson, W. M. Possible Significance of the Inhibitory Effect of Fever on Anaphylactic Phenomena. *J. Lab. & Clin. Med.*, 26:125 (Oct.), 1940.